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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
LONG, SCOTT	

ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/581,547	SCHLINGENSIEPEN ET AL.	
	Examiner	Art Unit	
	Scott D. Long	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14,18 and 20-28* is/are pending in the application.

4a) Of the above claim(s) *8-14,18 and 20-28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7* is/are rejected.

7)☒ Claim(s) *1, 4, 7* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *02 June 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/26/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Examiner acknowledges the election, without traverse, of Group I (claims 1-7) directed to a pharmaceutical composition comprising at least one TGF-beta antagonist and one cell proliferation inhibitor, in the reply filed on 14 April 2008.

Additionally, the examiner acknowledges receipt of the claim amendments submitted 4/14/2008.

Accordingly, the examiner hereby makes the restriction final.

Claim Status

Due to a typographical error, the originally filed claims did not include claim 24. Originally filed claims 25-29 were amended to become currently amended claims 24-28. Accordingly, claims 1-14, 18 and 20-28 are pending. However, claims 8-14, 18 and 20-28 are withdrawn from further consideration by the Examiner, pursuant to 37 CFR 1.142(b), as being drawn to non-elected inventions, there being no allowable generic or linking claim. Claims 1, 14, 18, 20-28 are amended. Claims 15-17 and 19 are canceled. Claims 1-7 are under current examination.

Sequence Compliance

Sequence Listing and CRF have been received and are acknowledged by examiner. A statement that the Computer Readable Form (CRF) and the Sequence Listing are identical has been submitted and is acknowledged by examiner.

Oath/Declaration

The oath or declaration, having the signatures of all inventors, received on 2 June 2006 is in compliance with 37 CFR 1.63.

Information Disclosure Statement

The Information Disclosure Statements (IDS) filed on 18 July 2007 consisting of 1 sheet(s) is/are in compliance with 37 CFR 1.97. Accordingly, examiner has considered the Information Disclosure Statements.

Priority

This application claims benefit as a PCT/EP04/53604 (filed 12/20/2004) which claims benefit of 60/541,771 (filed 02/05/2004). This application claims benefit from foreign application EPO 03029367.4 (filed 12/19/2003).

The instant application has been granted the benefit date, 19 December 2003, from foreign application EPO 03029367.4.

Specification

The specification is objected to because: The specification contains numerous instances of the phrase “Seq.Id.No.” According to the Sequence Rules described by 37

CFR 1.821(d), the proper form to indicate sequences is “SEQ ID NO:.” 37 CFR 1.821(d) states, “Where the description or claims of a patent application discuss a sequence that is set forth in the “Sequence Listing” in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the sequence identifier, preceded by “SEQ ID NO:” in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application.”

A full response to this Office Action must include an amendment to the specification, correcting this objectionable matter.

Claim Objections

Claim 1 is objected to because of the following informalities: Claim 1 recites the word, “(---RNA)." The examiner does not understand this term and believes it to be a typographical error; perhaps the applicant meant "(mRNA)."

Claims 1 and 7 are objected to because of the following informalities: Claims 1 and 7 contain the non-English spellings, “anti-progesterons,” and “estrogenes.” Claim 7 contains the non-English spellings, “hormone,” “alcaloid,” and “mifepriston.” Appropriate correction is required.

Claim 4 is objected to because of the following: Claim 4 recites the phrase, “Seq. ID. No. 1-146.” According to the Sequence Rules, this is improper form. 37 CFR 1.821(d) states, “Where the description or claims of a patent application discuss a sequence that is set forth in the “Sequence Listing” in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the sequence identifier,

preceded by "SEQ ID NO:" in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application."

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 4 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 4 is directed to pharmaceutical composition of claim 1, wherein the oligonucleotide comprises at least one of the sequences SEQ ID NO:1-147. According to the specification, pages 70-73, SEQ ID NO: 79-146 are oligonucleotides that hybridize to PGE, VEGF or IL-10 nucleic acids, rather that to any TGF-beta nucleic acid. Therefore, the examiner believes these sequences cannot be TGF-beta antagonists. This conflict, creates vague and unclear claim language.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-3 and 5-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Roth et al. (Cellular and Molecular Life Sciences. 1999; 56: 481-506).

Claim 1 is directed to a pharmaceutical composition comprising at least one TGF-beta antagonist, selected from the group of - oligonucleotides hybridising with an area of the messenger RNA (-RNA) and/or DNA encoding TGF-beta, - TGF-beta receptors and/or parts of them binding TGF-beta, - proteins, except antibodies, inhibiting TGF-beta - peptides of less than 100 kDa inhibiting TGF-beta - peptides being parts of TGF-beta and at least one substance inhibiting cell proliferation and/or inducing cell death, selected from the group of temozolomide, nitrosoureas, Vinca alkaloids, antagonists of the purine and pyrimidine bases, cytostatic active antibiotics, caphthotecine derivatives, anti-androgens, anti-estrogens, anti-progesterons and analogs of gonadotropin releasing-hormone. The examiner does not understand the

meaning of "(---RNA)." The specification has numerous instances of "m-RNA." Therefore, the examiner interprets "---RNA" to mean "mRNA." Roth et al. teach "great efforts are being made to enhance antitumoral efficacy by combining various cytotoxic agents, by novel routes of drug administration, or by combining anticancer drugs and immune modulators." (page 481, abstract). Roth et al. teach "experimental drugs for the treatment of malignant gliomas…Temozolomide" (page 486, Table 2). Roth et al. teach "catagories of immunotherapy for malignant glioma…inihibition of immunosuppressive factors, e.g, TGF-β by antisense TGF-β" (page 486, Table 3).

Claim 2 is directed to the pharmaceutical composition of claim 1, wherein both agents mixed together. Roth et al. teach combination therapies which are simultaneously administered.

Claim 3 is directed to the pharmaceutical composition of claim 1, wherein both agents are separate. Roth et al. teach combination therapies in which it is not desirable for simultaneously administration. Roth et al. also teach strategies which are based on alternative routes of drug administration.

Claim 7 is directed to the pharmaceutical composition according to claim 1 wherein - the nitrosourea is selected from the group of ACNU, BCNU and CCNU, - the Vinca-alcaloid is selected from. the group of vinblastine, vincristine, vindesine, - the antagonist of the purine and pyrimidine bases is selected from the group of 5-fluorouracile, 5-fluorodeoxiuridine, cytarabine and gemcitabine, - the cytostatic antibiotic is selected from the group of doxorubicine and liposomal PEGylated

doxorubicin, - the camphthotecine derivative is selected from the group of irinotecane and topotecane, - the anti estrogenes are selected from the group of tamoxifen, exemestane, anastrozole and fluvestrant, - the antiandrogens are selected from the group of flutamide and bicalutamide, - the antiprogesterons are selected from the group of mifepriston - the analogs of gonadotropin releasing horrnon are selected from the group of leuprolide and gosereline. Roth et al. teach numerous members of the Markush group recited in claim 7, including BCNU, vincristine, 5-FU and tamoxifen.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to combine antisense TGF-beta oligonucleotides with at least one substance inhibiting cell proliferation and/or inducing cell death in a pharmaceutical composition.

The person of ordinary skill in the art would have been motivated to make those modifications because Roth et al. teaches that combination therapies comprising antisense TGF-beta oligonucleotides and at least one substance inhibiting cell proliferation and/or inducing cell death are desirable and known in the art.

The skilled artisan would have had a reasonable expectation of success in making a pharmaceutical composition because these active ingredients are known in the art.

Therefore the pharmaceutical composition as taught by Roth et al. would have been *prima facie* obvious over the pharmaceutical composition of the instant application.

Claims 1-3 and 5-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Roth et al. (Cellular and Molecular Life Sciences. 1999; 56: 481-506) in view of Jachimczak et al. (Int. J. Cancer. 1996; 65: 332-337).

Claim 1 is directed to a pharmaceutical composition comprising at least one TGF-beta antagonist, selected from the group of - oligonucleotides hybridising with an area of the messenger RNA (-RNA) and/or DNA encoding TGF-beta, - TGF-beta receptors and/or parts of them binding TGF-beta, - proteins, except antibodies, inhibiting TGF-beta - peptides of less than 100 kDa inhibiting TGF-beta - peptides being parts of TGF-beta and at least one substance inhibiting cell proliferation and/or inducing cell death, selected from the group of temozolomide, nitrosoureas, Vinca alkaloids, antagonists of the purine and pyrimidine bases, cytostatic active antibiotics, caphthotecine derivatives, anti-androgens, anti-estrogens, anti-progesterons and analogs of gonadotropin releasing-hormone. The examiner does not understand the meaning of "(---RNA)." The specification has numerous instances of "m-RNA." Therefore, the examiner interprets "---RNA" to mean "mRNA." Roth et al. teach "great efforts are being made to enhance antitumoral efficacy by combining various cytotoxic agents, by novel routes of drug administration, or by combining anticancer drugs and immune modulators." (page 481, abstract). Roth et al. teach "experimental drugs for the treatment of malignant gliomas…Temozolomide" (page 486, Table 2). Roth et al. teach

"catagories of immunotherapy for malignant glioma…inihibition of immunosuppressive factors, e.g, TGF-β by antisense TGF-β" (page 486, Table 3).

Claim 2 is directed to the pharmaceutical composition of claim 1, wherein both agents mixed together. Roth et al. teach combination therapies which are simultaneously administered.

Claim 3 is directed to the pharmaceutical composition of claim 1, wherein both agents are separate. Roth et al. teach combination therapies in which it is not desirable for simultaneously administration. Roth et al. also teach strategies which are based on alternative routes of drug administration.

Claim 4 is directed to the pharmaceutical composition according to claim 1, wherein the oligonucleotide comprises at least one of the sequences selected from the group consisting of SEQ ID NO:1-146. Jachimczak et al. teach an antisense oligonucleotide against TGF-β1 with the sequence CGATAGTCTTGCAG. The sequence taught by Jachimczak et al. is 100% identical to SEQ ID NO:1 of the instant application. Jachimczak et al. teach that such oligonucleotides can be used to inhibit expression of the target protein.

Claim 5 is directed to the pharmaceutical composition according to claim 4 wherein at least one nucleotide of the oligonucleotide is modified at the sugar moiety, the base and/or the internucleotide linkage. Claim 6 is directed to the pharmaceutical composition according to claim 5 wherein at least one modified internucleotide linkage is a phosphorothioate linkage. Jachimczak et al. teach employing phosphorothioate

antisense oligodeoxynucleotides…specifically targeted against the coding sequences of TGF-β1 mRNA" (page 332, abstract).

Claim 7 is directed to the pharmaceutical composition according to claim 1 wherein - the nitrosourea is selected from the group of ACNU, BCNU and CCNU, - the Vinca-alcaloid is selected from. the group of vinblastine, vincristine, vindesine, - the antagonist of the purine and pyrimidine bases is selected from the group of 5-fluorouracile, 5-fluorodeoxiuridine, cytarabine and gemcitabine, - the cytostatic antibiotic is selected from the group of doxorubicine and liposomal PEGylated doxorubicin, - the camphthotecine derivative is selected from the group of irinotecane and topotecane, - the anti estrogenes are selected from the group of tamoxifen, exemestane, anastrozole and fluvestrant, - the antiandrogens are selected from the group of flutamide and bicalutamide, - the antiprogesterons are selected from the group of mifepriston - the analogs of gonadotropin releasing horrnon are selected from the group of leuprolide and gosereline. Roth et al. teach numerous members of the Markush group recited in claim 7, including BCNU, vincristine, 5-FU and tamoxifen.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to use the phosphorothioate antisense oligonucleotide having the sequence CGATAGTCTTGCAG in a pharmaceutical composition comprising a combination of antisense TGF-beta oligonucleotides with at least one substance inhibiting cell proliferation and/or inducing cell death in a pharmaceutical composition.

The person of ordinary skill in the art would have been motivated to make those modifications because Jachimczak et al. teach phosphorothioate antisense

oligonucleotide have enhanced stability (page 332, col.2, parag.1) and CGATAGTCTTGCAG inhibits cell proliferation in gliomas (abstract)

The skilled artisan would have had a reasonable expectation of success in making a pharmaceutical composition because these active ingredients are known in the art.

Therefore the pharmaceutical composition as taught by Roth et al. in view of Jachimczak et al. would have been *prima facie* obvious over the pharmaceutical composition of the instant application.

Conclusion

No claims are allowed.

Examiner Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Scott Long** whose telephone number is **571-272-9048**. The examiner can normally be reached on Monday - Friday, 9am - 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph Woitach** can be reached on **571-272-0739**. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/SDL/ Scott Long
Patent Examiner, Art Unit 1633

/Janet L. Epps-Ford/
Primary Examiner, Art Unit 1633